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ORIGINAL ARTICLE

Pylorus-preserving gastrectomy for early cancer involving the upper third: can we go higher?

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Abstract

Background Pylorus-preserving gastrectomy (PPG) is commonly performed for early gastric cancer (EGC) located in middle third of the stomach. We investigated the surgical, oncological, and functional outcomes of PPG involving the upper third of stomach.

Methods We included all patients of the period 2013–2016 who underwent PPG, distal subtotal gastrectomy (DSG), and total gastrectomy (TG) for EGC involving the upper third by carefully defining the localization. Surgical, oncological, and functional outcome analyses included postoperative morbidity, lymph-node metastasis, tumor recurrence, postoperative body weight, body mass index, hemoglobin, total protein, albumin, quantification of intraabdominal fat, and gallstone development.

Results Overall, 288 cases were analyzed: 145 PPG, 61 DSG, and 82 TG. In the study period, patients potentially underwent PPG for EGC involving the upper third, if enough proximal remnant stomach was found whilst achieving a sufficient proximal margin. PPG resulted in less operation time ($p < 0.001$), less blood loss ($p = 0.002$) and lower postoperative morbidity compared to TG. For lymph-node (LN) stations being resected in all groups, no difference was found in number of resected LN. Recurrence-free survival was similar for all groups. PPG showed advantages regarding postoperative body weight, hemoglobin, total protein, albumin in postoperative 6 and 12 month follow-up. Lowest decrease of abdominal fat area after 12 months was seen for PPG. Gallstone incidence was significantly lower after PPG compared to TG ($p < 0.001$).

Conclusions For EGC involving the upper third, PPG can be another good option with lower postoperative morbidity, better functional outcomes, and same oncological safety.

Keywords Pylorus-preserving gastrectomy · Upper stomach · Early gastric cancer · Outcomes

Introduction

Although gastric cancer is still one of the leading causes of cancer deaths [1], its prognosis has been significantly improved in several eastern countries due to the early detection [2], especially in Korea and Japan [3, 4]. Gastrectomy with standardized lymph-node dissection was established as a standard treatment for the early gastric cancer (EGC), which resulted in a significant improvement of survival

Chun-Chao Zhu and Hui Cao have contributed equally to this work.

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rate. For early gastric cancer, surgeons started to consider functional preserving gastrectomy to improve the functional outcome and quality of life (QOL) without compromising oncological safety [5–10]. Pylorus-preserving gastrectomy (PPG) is such kind of function-preserving surgery, which has gained popularity in East Asian countries [5, 11–13]. PPG has become an optional method in Japanese Gastric Cancer Treatment Guideline for tumor located in the middle third portion of the stomach [14]. However, "middle third portion" is an anatomic definition [15], which cannot be precisely identified in preoperative inspection.

The early cancers located in the distal part of the upper third stomach would by definition give an indication for total gastrectomy (TG) or proximal gastrectomy (PG) but technically could be resected without sacrificing the cardia (Supplementary Fig. 1). Such operation was originally established as distal subtotal gastrectomy (DSG). This operation may be considered insufficient for more advanced cancers in terms of omitted removal of nearby lymph nodes best exemplified by LN station #2. For the population of early gastric cancer, in which oncological safety in terms of adequate lymphadenectomy through DSG can be ensured, resection of distal lymph nodes such as LN stations #5 may be less important in this tumor location. PPG could be evaluated as an option in this situation, as it is suggested to come along with favorable functional outcomes compared to DSG.

Any resection type should achieve a margin free of tumor, which can be confirmed by frozen biopsy. Currently, the localization of the primary tumor is commonly assessed by pre- and intraoperative endoscopy and radiography, which determines the extend of resection [16, 17]. These factors mostly contribute to the oncological safety of PPG in EGC of the upper stomach.

In this study, we aimed to evaluate the surgical, oncological, and functional outcome of PPG operation in selected cT1 cases of tumor located in the upper portion of the stomach compared to distal subtotal gastrectomy (DSG) and total gastrectomy (TG) outcomes of equally located tumors.

Methods

Patients

Patients of this study were identified from our prospectively collected database between January 2013 and December 2016 in Seoul National University Hospital. The stage of the tumor was classified according to the seventh edition of AJCC TNM classification. Patients were included with biopsy proven, clinically early gastric adenocarcinoma, so cT1N0M0 staging. The most important step was to identify patients with the desired tumor location, which is located more proximal than the usual location for PPG operation.

Definition of location: (1) included, if tumor involved the upper third of the stomach, which was identified by preoperative endoscopy and postoperative pathology; (2) excluded, if the proximal tumor border was less than 3 cm apart from esophagogastric junction (EGJ); or distal tumor border less than 4 cm apart to pylorus clinically. This exclusion was done to exclude diffuse cancers that had to be treated by TG and tumors that were too close to the junction to be resected by PPG or DG. This definition clearly distinguished the patient selection from previously published PPG patient cohorts, in which the tumor location was within the middle third of the stomach [7]. To make the oncological outcome data comparable, we integrated the following exclusion criteria: history of previous abdominal surgery; metachronous and synchronous malignancy.

For patients who underwent PPG or DSG, preoperative endoscopy was performed for tumor localization; metal clips were used to mark the proximal and distal tumor border. Intraoperative frozen biopsy was done in all the cases to confirm the proximal and distal resection margin.

Surgical procedure of PPG

Most of the PPG cases were performed laparoscopically and robotically. Important steps of the procedure included preserving a decent antral cuff length (≥ 3 cm) and preserving infrapyloric vessels. Lymph-node dissection included station 1, 3, 4sb, 4d, 6, 7 for D1 dissection and additional No.8a and 9 for D1 + dissection. In 119 out of 145 cases (82.1%), #11p LN dissection was also performed. The length of preserved antrum cuff ranged from at least 3 cm up to 5 cm depending on the operator`s decision, which was mainly driven by the distance from distal tumor margin to pylorus and then the size of the proximal remnant stomach. Almost all cases (143/145, 98.6%) were performed by extracorporeal gastro-gastrostomy with hand-sewing. This technique provides the possibility to touch metal clips indicating the proximal and distal tumor margin. These clips were applied by preoperative endoscopy, so the margin safety of PPG cases could be guaranteed. Furthermore, rotation of the stomach for proximal transaction to provide a more sufficient margin (which is described below) can only be carried securely extracorporeally.

PPG operation was modified in contribution to the tumor location: (1) as LN station #1 which was close to the tumor, the surgeons liberally removed #1 lymph node for oncology safety, although it may compromise hepatic branch of vagus nerve. (2) If the tumor was located at the anterior wall or posterior wall, rotation of the gastric body before transection was performed in order to bring the lesion on "new lesser curvature side". This maneuver provides a longer proximal resection margin when applying the linear stapler for cutting the proximal side of the specimen (Supplementary Fig. 2).

In most cases of DSG and TG, surgery was performed minimally invasive. Regarding the reconstruction method, in DSG, 24 patients underwent Billroth II anastomosis (17 of 24 cases, underwent additional Braun J-Jstomy); another 37 patients underwent Roux-en-Y anastomosis (2 of 37 patients underwent uncut Roux-en-Y anastomosis). For the TG group, in all 82 cases, a Roux-en-Y anastomosis was performed.

Surgical and oncological outcomes

For our prospectively collected database from January 2013 to December 2016 in Seoul National University Hospital, the following clinical data were collected and analyzed: age, sex, body mass index (BMI), surgical approach, combined cholecystectomy, operator, tumor size, histological type, and postoperative TNM stage. Clinicopathological characteristics using the Japanese Classification of Gastric Cancer and the seventh edition of American Joint Committee on Cancer (AJCC) TNM classification were compared among PPG, DSG, and TG groups [15, 18]. Surgical outcomes included operation time, blood loss, postoperative stay, proximal/distal resected margin, and number of resected and metastatic LN. All postoperative complications had been prospectively collected and reported in the weekly based tumor board at Seoul National University Hospital. The severity of complications was classified according to the Clavien–Dindo classification system [19, 20]. Recurrence-free survival was determined by reviewing the results of the patient's regular follow-up appointment, including CT scan, ultrasound, and esophagogastroduodenoscopy which were taken periodically based on the standard schedule. Each station of lymph nodes was routinely separated from surgical specimen before pathologic inspection. Resected and metastatic lymph-node data were obtained from postoperative pathological report.

Nutritional and functional outcomes

To evaluate the postoperative nutritional status, we collected and analyzed the body weight, BMI, and serological parameter (hemoglobin, total protein and albumin) preoperatively and 6 and 12 months after operation. Abdominal adipose tissue was measured using preoperative and 1-year postoperative CT scan and processed by Image J program (National Institute of Health, NIH, USA). To measure total abdominal and visceral fat areas, a 5-mm CT slice scan was acquired at the L3–L4 level with the subject at supine position [21]. The region of interest was from -250 to -50 Hounsfield unit [22, 23]. The visceral fat area was defined by the internal aspect of the abdominal and oblique muscle walls surrounding the cavity and the posterior aspect of the vertebral body. The subcutaneous fat area was calculated by subtracting the visceral fat area from the total abdominal fat area. The rates of total, visceral, and subcutaneous fat loss 1 year after operation were compared.

Gallbladder stones after operation were diagnosed by routine follow-up abdominal CT scan or ultrasonography.

Statistics

Statistical analyses were performed using SPSS 20.0 (SPSS Inc, Chicago, IL, USA) and GraphPad Prism 7 (San Diego, CA, USA) software. Patient characters and surgical complication were compared using Chi-square test. Surgical data, resected lymph nodes, and nutritional and abdominal fat data were compared using Student *t* test. Binary logistic regression analysis was used in the calculation of risk factor of postoperative morbidity. Recurrence-free survival and cumulative incidence of gallstones were calculated according to Kaplan–Meier method, and log-rank test was used for comparing the survival distributions. Independent risk factors for postoperative morbidity were evaluated by logistic regression analysis. All statistical tests were two-sided. p value less than 0.05 was considered statistically significant.

Results

Patient characteristics

In the period of the study, regardless of tumor localization, 587 PPG operations were performed in this center. Overall, we identified 344 patients with EGC involving the upper third of the stomach for all resection types. After applying the inclusion and exclusion criteria for the upper third EGC cases, we identified 288 cases as the final study cohort. Among these eligible cases, 145 patients underwent PPG operation, 61 patients underwent DSG operation, and 82 patients underwent TG operation. Detailed characteristics of these 288 cases are shown in Table 1. Chi-square test revealed a significantly higher proportion of female patients in PPG than in TG group. There was no significant difference of age, BMI, tumor location (circular), surgical approach, tumor size, combined cholecystectomy, and pathological tumor stage; patients whose pathologic stage 2 or 3 received 8 cycles of adjuvant chemotherapy using XELOX (Oxaliplatin plus Xeloda) or SOX (Oxaliplatin plus S1).

Surgical outcomes

Surgical data analysis is also shown in Table 1, which revealed that mean operation time ($p < 0.001$) and mean estimated blood loss ($p = 0.002$) of PPG patients were significantly lower compared to the TG group. PPG group had shorter proximal/distal margin than both DSG ($p = 0.008$, $p < 0.001$) and TG group ($p < 0.001$, $p < 0.001$).

Table 1 Patients' characteristics and surgical data ($n=288$)

Characteristics	PPG, $n=145$ (%)	DSG, $n=61$ (%)	TG, $n=82$ (%)	p value[a]	p value[b]
Age				0.520	0.790
≥65	47 (32.4)	17 (27.9)	28 (34.1)		
<65	98 (67.6)	44 (72.1)	54 (65.9)		
Sex				0.212	**0.002**
Male	67 (46.2)	34 (55.7)	55 (67.1)		
Female	78 (53.8)	27 (44.3)	27 (32.9)		
BMI				0.168	0.312
≥25	32 (22.1)	19 (31.1)	23 (28.0)		
<25	113 (77.9)	42 (68.9)	59 (72.0)		
Tumor location (circular)				0.699	0.224
LC	49 (33.8)	18 (29.5)	20 (24.4)		
GC	23 (15.9)	7 (11.5)	11 (13.4)		
AW	27 (18.6)	13 (21.3)	14 (17.1)		
PW	46 (37.2)	23 (37.7)	37 (45.1)		
Surgical approach				0.415	0.264
Laparoscopic	111 (76.5)	48 (78.7)	62 (75.6)		
Robotic	31 (21.4)	10 (16.4)	15 (18.3)		
Open	3 (2.1)	3 (4.9)	5 (6.1)		
Combined cholecystectomy				0.455	0.328
Yes	11 (7.6)	7 (11.5)	10 (12.2)		
No	134 (92.4)	54 (88.5)	72 (87.8)		
Tumor size				0.591	0.068
<2 cm	75 (51.7)	27 (44.3)	33 (40.2)		
2–5 cm	65 (44.8)	31 (50.8)	41 (50.0)		
≥5 cm	5 (4.5)	3 (4.9)	8 (9.8)		
Histological type				0.888	0.566
Differentiated	65 (44.8)	28 (45.9)	40 (48.8)		
Undifferentiated	80 (55.2)	33 (54.1)	42 (51.2)		
T stage				0.107	0.058
T1a	75 (51.7)	27 (44.3)	34 (41.5)		
T1b	57 (39.3)	31 (50.8)	39 (47.5)		
T2	13 (9.0)	2 (3.3)	6 (7.3)		
T3	0 (0.0)	1 (1.6)	3 (3.7)		
N stage				0.341	0.470
N0	131 (90.3)	51 (83.7)	77 (93.9)		
N1	7 (4.8)	6 (9.8)	3 (3.7)		
N2	3 (2.1)	3 (4.9)	2 (2.4)		
N3	4 (2.8)	1 (1.6)	0 (0.0)		
TNM (7th AJCC)				0.430	0.423
p Stage I	138 (95.2)	56 (91.7)	79 (96.3)		
p Stage II	4 (2.8)	4 (6.7)	2 (3.7)		
p Stage III	3 (2.0)	1 (1.6)	0 (0.0)		
Operation time (min)	216 ± 57	222 ± 65	264 ± 66	0.493	**<0.001**
Blood loss (ml)	110 ± 123	132 ± 137	170 ± 150	0.266	**0.002**
Postoperative stay (days)	9.8 ± 6.7	12.6 ± 18.5	11.4 ± 12.7	0.262	0.138
PRM (cm)	2.3 ± 1.3	2.9 ± 1.7	4.1 ± 1.5	**0.008**	**<0.001**
DRM (cm)	5.8 ± 2.7	9.8 ± 3.3	11.3 ± 3.5	**<0.001**	**<0.001**
Resected LN	35.1 ± 14.0	39.8 ± 14.0	45.7 ± 17.2	**0.027**	**<0.001**

Statistical significant values are shown in bold

[a]Comparison of PPG group and DSG group

[b]Comparison of PPG group and TG group

Postoperative morbidity analysis (Table 2) showed that PPG had the lowest complication rate in each category which was only significant in grade II, where TG patients showed a significant higher morbidity than the PPG group ($p = 0.011$). PPG group had a similar incidence of delayed gastric emptying (DGE) compared to DSG group (3.4% vs 3.3%, $p = 1.000$). For total complication rate, PPG also resulted in the lowest incidence (12.4% vs 18.0% vs 22.0%), which was significantly lower than TG group when excluding DGE (9.0% vs 22.0%, $p = 0.006$). There was no postoperative mortality in each group. Table 3 shows that, among all clinical features, operation type of total gastrectomy was an independent risk factor for the postoperative complication except delayed gastric emptying ($p = 0.015$, odds ratio = 3.006, 95.0% confidence interval = 1.238–7.300).

Oncological outcomes

Although the total number of resected LN in PPG group was lower compared to those in DSG ($p = 0.027$) and TG group ($p < 0.001$), there was no difference in resected LN for the stations among PPG or TG except those stations (#2, #4sa, and #5) which are omitted in PPG (Table 4). The mean number of resected lymph nodes at #6 station, where right gastroepiploic vessels are preserved in PPG group, was similar to DSG and TG group (5.9 vs 6.3 vs 6.4, $p = 0.279$, 0.224).

Table 2 Surgery-related complication

Complications	PPG, $n = 145$ (%)	DSG, $n = 61$ (%)	TG, $n = 82$ (%)	p value[a]	p value[b]
Events with complication					
Grade I	4 (2.8)	3 (4.9)	6 (7.3)	0.425	0.175
Wound	1 (0.7)	1 (1.6)	0 (0.0)		
Ileus/motility disorder	2 (1.4)	1 (1.6)	2 (2.4)		
Pulmonary	1 (0.7)	0 (0.0)	0 (0.0)		
Fluid collection	0 (0.0)	0 (0.0)	1 (1.2)		
Liver dysfunction	0 (0.0)	0 (0.0)	1 (1.2)		
Ischemia	0 (0.0)	0 (0.0)	1 (1.2)		
Luminal bleeding	0 (0.0)	0 (0.0)	1 (1.2)		
Other infection	0 (0.0)	1 (1.6)	1 (1.2)		
Grade II	5 (3.4)	5 (8.2)	10 (12.2)	0.148	**0.011**
Ileus/motility disorder	3 (2.1)	0 (0.0)	2 (2.2)		
Pulmonary	1 (0.7)	0 (0.0)	3 (2.9)		
Delayed gastric emptying	1 (0.7)	1 (1.6)	0 (0.0)		
Anastomosis leakage	1 (0.7)	1 (1.6)	1 (1.2)		
Fluid collection	1 (0.7)	0 (0.0)	1 (1.2)		
Fistula	0 (0.0)	1 (1.6)	1 (1.2)		
Luminal bleeding	0 (0.0)	0 (0.0)	1 (1.2)		
Cardiac	0 (0.0)	0 (0.0)	2 (2.4)		
Other infection	0 (0.0)	1 (1.6)	1 (1.2)		
Neuropsychic	0 (0.0)	1 (1.6)	0 (0.0)		
Grade IIIa	9 (6.2)	5 (8.2)	5 (6.1)	0.604	0.974
Wound	3 (2.1)	0 (0.0)	1 (1.2)		
Delayed gastric emptying	4 (2.8)	1 (1.6)	0 (0.0)		
Anastomosis leakage	1 (0.7)	3 (4.9)	2 (2.4)		
Fluid collection	1 (0.7)	1 (1.6)	1 (1.2)		
Pulmonary	0 (0.0)	1 (1.6)	2 (2.4)		
Grade IIIb	0 (0.0)	0 (0.0)	1 (1.2)	N/A	0.361
Ileus	0 (0.0)	0 (0.0)	1 (0.7)		
Number of patients					
Total cases of all complications	18 (12.4)	11 (18.0)	18 (22.0)	0.290	0.059
Delayed gastric emptying	5 (3.4)	2 (3.3)	N/A	1.000	N/A
Except for DGE	13 (9.0)	10 (16.4)	18 (22.0)	0.122	**0.006**

Statistical significant values are shown in bold

[a]Comparison of PPG group and DSG group

[b]Comparison of PPG group and TG group

Table 3 Risk factors of postoperative morbidity by multivariate analysis

Variables	Complication		Complication except for DGE	
	95% CI	*p* value	95% CI	*p* value
Age (vs ≥ 65)	1.445 (0.712–2.933)	0.309	1.205 (0.558–2.601)	0.635
Sex (vs female)	0.794 (0.387–1.628)	0.529	0.913 (0.420–1.985)	0.818
BMI (vs ≥ 25)	0.844 (0.393–1.813)	0.663	1.009 (0.449–2.266)	0.982
Operation time (min)	1.000 (0.994–1.006)	0.997	0.998 (0.991–1.005)	0.600
Blood loss (ml)	0.999 (0.996–1.002)	0.474	0.999 (0.996–1.002)	0.550
Combined cholecystectomy	1.610 (0.548–4.728)	0.386	1.625 (0.516–5.121)	0.407
Operation type (PPG)		0.347		0.051
vs DSG	1.427 (0.546–3.732)	0.468	1.578 (0.548–4.544)	0.398
vs TG	1.827 (0.806–4.138)	0.149	3.006 (1.238–7.300)	**0.015**

Statistical significant values is shown in bold

Table 4 Lymph-node resection and metastasis information by station

LN station	Resected number					Metastatic rate			
	PPG (*n* = 145)	DG (*n* = 61)	TG (*n* = 82)	*p* value[a]	*p* value[b]	PPG (*n* = 145)	DG (*n* = 61)	TG (*n* = 82)	Total
#1	4.3 ± 3.4	4.2 ± 3.7	5.1 ± 4.0	0.772	0.145	2.8% (4/145)	3.2% (2/61)	0.0% (0/82)	2.1% (6/288)
#2	N/A	N/A	3.2 ± 2.3			N/A	N/A	0.0% (0/82)	0.0% (0/82)
#3	4.7 ± 4.0	5.4 ± 3.7	5.9 ± 5.2	0.276	0.083	4.8% (7/145)	4.9% (3/61)	0.0% (0/82)	3.5% (10/288)
#4sa	N/A	N/A	1.3 ± 2.4			0.0% (0/21)	0.0% (0/8)	0.0% (0/82)	0.0% (0/111)
#4sb	1.2 ± 2.1	0.9 ± 1.8	1.3 ± 2.0	0.332	0.750	0.7% (1/145)	1.6% (1/61)	0.0% (0/82)	0.7% (2/288)
#4d	6.3 ± 4.5	7.0 ± 5.4	7.6 ± 5.2	0.293	0.069	2.8% (4/145)	1.6% (1/61)	0.0% (0/82)	1.7% (5/288)
#5	N/A	0.7 ± 1.0	1.2 ± 1.9			0.0% (0/13)	0.0% (0/61)	0.0% (0/82)	0.0% (0/156)
#6	5.9 ± 3.5	6.3 ± 3.4	6.4 ± 3.7	0.279	0.244	0.0% (0/145)	3.3% (2/61)	0.0% (0/82)	0.7% (2/288)
#7	4.9 ± 3.4	5.1 ± 3.6	3.9 ± 3.0	0.621	0.052	4.1% (6/145)	4.9% (3/61)	1.2% (1/82)	3.8% (11/288)
#8a	3.8 ± 2.1	3.7 ± 3.2	3.6 ± 2.4	0.714	0.598	0.7% (1/139)	1.7% (1/60)	0.0% (0/82)	0.7% (2/281)
#9	3.0 ± 2.5	3.6 ± 2.5	3.1 ± 2.3	0.136	0.709	2.8% (4/142)	3.3% (2/60)	0.0% (0/82)	2.1% (6/284)
#10	N/A	N/A	N/A			0.0% (0/4)	N/A	0.0% (0/24)	0.0% (0/28)
#11p	2.1 ± 2.2	2.8 ± 2.6	2.2 ± 2.4	0.102	0.818	0.8% (1/119)	0.0% (0/49)	0.0% (0/77)	0.4% (1/245)
#11d	N/A	N/A	N/A			0.0% (0/6)	0.0% (0/1)	0.0% (0/51)	0.0% (0/58)
#12	N/A	N/A	N/A			0.0% (0/2)	0.0% (0/22)	0.0% (0/14)	0.0% (0/38)
Total	35.1 ± 14.0	39.8 ± 14.0	45.7 ± 17.2	**0.027**	**< 0.001**				

Statistical significant values are shown in bold

N/A not assessable because of limited number of cases

[a]Comparison of PPG group and DG group

[b]Comparison of PPG group and TG group

The mean number of resected lymph node at no. 1 station was also similar to DSG and TG group (4.3 vs 4.2 vs 5.1, $p = 0.772, 0.145$).

According to the pathological result the lymph-node metastasis rate in #2, #4sa, and #5 station, where dissection is mostly omitted in PPG, was 0.0% in all the available cases among all groups, as also shown in Table 4.

During follow-up, 6 patients with recurrence were identified: 2 patients in the PPG group, 1 in DSG group and 3 in TG group. Neither anastomotic site nor regional lymph-node recurrences have been found in PPG group. Detailed information of recurrent cases is shown in Supplementary Table 1. 3-year recurrence-free survival rate of PPG group was similar to DSG and TG groups (97.8% vs 94.4% vs 95.9%, $p = 0.423$, Fig. 1); median follow-up period was 30 months for PPG groups, 24 months for DSG group, and 26.5 months for TG group.

Nutritional and functional outcomes

The PPG patients showed a lower decrease of body weight, BMI, hemoglobin, total protein, and albumin comparing preoperative values 6 and 12 months postoperatively. Detailed mean values and *p* values are shown in Table 5.

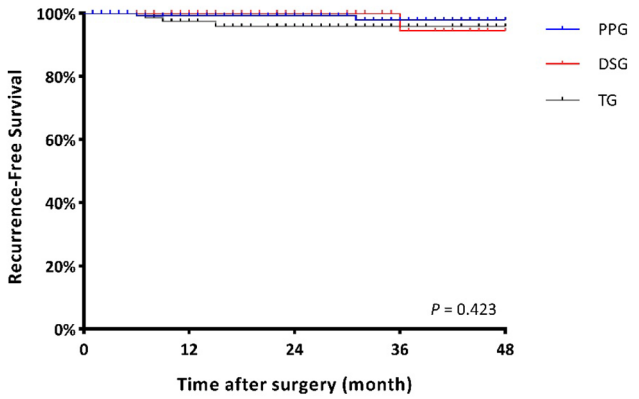

Fig. 1 Recurrence-free survival after PPG, DSG, and TG

Difference of abdominal fat proportion of the subgroups 1 year after operation is shown in Fig. 2a. Mean decreasing rates of total fat (−39.8% vs −30.2%, $p=0.047$) and visceral fat (−49.8% vs −38.6%, $p=0.049$) in the DSG group were significantly higher than in the PPG group. Mean decrease of total fat (−54.4% vs −30.2%, $p<0.001$), visceral fat (−66.4% vs −38.6%, $p<0.001$), and subcutaneous fat (−44.6% vs −23.9%, $p<0.001$) was significantly higher after TG compared to PPG.

Cumulative curve (Fig. 2b) shows 3-year cumulative incidence of gallbladder stones of the TG group which is much higher than of the PPG group (30.7% vs 3.2%, $p<0.001$).

Table 5 Changed value of nutrition parameters of different type of gastrectomy

Changed value	PPG ($n=129$)	DSG ($n=51$)	TG ($n=69$)	p value[a]	p value[b]
Body weight (kg)					
Postoperative 6 months	−4.3 ± 4.1	−6.4 ± 4.5	−7.6 ± 4.9	**0.007**	**< 0.001**
Postoperative 12 months	−3.8 ± 4.9	−5.1 ± 10.5	−8.0 ± 5.5	0.285	**< 0.001**
BMI (kg/m^2)					
Postoperative 6 months	−1.7 ± 1.7	−2.3 ± 1.7	−2.8 ± 1.7	**0.032**	**< 0.001**
Postoperative 12 months	−1.5 ± 2.0	−1.9 ± 4.2	−2.9 ± 2.0	0.485	**< 0.001**
Hemoglobin (g/dL)					
Postoperative 6 months	−0.5 ± 1.2	−1.1 ± 1.0	−1.4 ± 1.1	**0.002**	**< 0.001**
Postoperative 12 months	−0.2 ± 1.2	−0.8 ± 1.0	−1.2 ± 1.4	**0.001**	**< 0.001**
Total protein (g/dL)					
Postoperative 6 months	0.1 ± 0.5	−0.2 ± 0.5	−0.4 ± 0.4	**< 0.001**	**< 0.001**
Postoperative 12 months	0.0 ± 1.2	−0.3 ± 0.5	−0.5 ± 0.9	0.059	**0.003**
Albumin (g/dL)					
Postoperative 6 months	−0.0 ± 0.4	−0.2 ± 0.3	−0.2 ± 0.3	**0.001**	**< 0.001**
Postoperative 12 months	−0.1 ± 0.7	−0.2 ± 0.3	−0.3 ± 0.6	0.197	**0.042**

Statistical significant values are shown in bold

[a]Comparison of PPG group and DSG group

[b]Comparison of PPG group and TG group

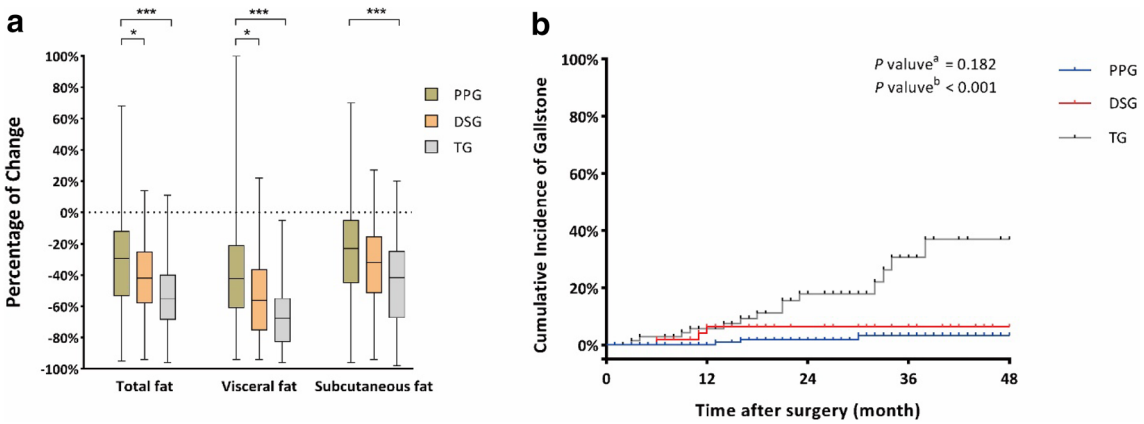

Fig. 2 Nutritional/functional outcomes: **a** decreased rate of abdominal fat 1 year after operation (*< 0.05, ***< 0.001); **b** cumulative incidence of gallbladder stone (**a** comparison of PPG group and DSG group; **b** comparison of PPG group and TG group)

Discussion

Early gastric cancer has a low recurrence rate and a good prognosis after appropriate surgical treatment. More and more surgeons contribute their efforts to function-preserving surgical procedure and progression is recognized on improving the postoperative quality of life (QOL) for EGC patients. Preserving more remnant stomach can influence the gastric function after surgery. Even for upper third gastric cancer, distal subtotal gastrectomy can be performed in suitable cases [5, 24, 25]. Compared to total gastrectomy, DSG leads to better nutritional and function outcomes and can improve QOL [26, 27]. Nonetheless, PPG, as a typical function-preserving gastrectomy, has been demonstrated to show further advantages in functional outcomes compared to distal gastrectomy in middle third EGC [7, 28, 29]. In addition, the oncological safety of PPG operation has been demonstrated in large retrospective studies [7, 9, 30]. To gain more evidence about the functional outcome, KLASS-04, a multicenter randomized-controlled trial comparing laparoscopic pylorus-preserving gastrectomy (LPPG) versus laparoscopic distal gastrectomy (LDG) for the middle third early gastric cancer has finished recruitment in Korea [11].

According to the recommended indication [14, 30], middle third EGC is suitable for PPG operation, providing a good feasibility to preserve the proximal stomach and the antral cuff with a tumor-free resection margin. Clinically, lower gastric body tumor location may represent the optimal tumor location to perform PPG operation. However, there are some mid body or high body EGC cases, which involve the upper middle third of the stomach, still having enough distance from EGJ to obtain a proximal remnant stomach and the cardia, which opens the option for DSG and for PPG in the early gastric cancer. In this setting, application of preoperative endoscopic marking of tumor border makes the resected margin much safer when performing PPG or other stomach-preserving gastrectomy [31]. From January 2013 to December 2016, we have performed 587 cases of PPG operation; in 145 of them, the tumor was located or involved the upper third of the stomach. In our cohort of PPG and DSG, preoperative endoscopy localization and intraoperative margin frozen biopsy were routinely applied. Between 2013 and 2016, there were only 2 cases of PPG and 2 cases of DSG cases converted to total gastrectomy because of positive margin. With the aid of preoperative endoscopic localization and intraoperative frozen section margin assessment, we were able to maximumly preserve the remnant stomach while keeping the oncological safety in some selected patient with EGC in upper stomach.

Another important concern before applying PPG for these highly located cancer cases was the oncological safety regarding lymph-node metastases. Most importantly safety could be demonstrated for LN station #2 by reviewing the institutions' own database with 4660 cases between 2003 and 2013 (Supplementary table 2). Data showed sufficient safety for LN station #2 for the early cancers located in midbody and high body. A previously published study also showed low metastatic rate of these LN stations in middle or upper third EGC [32]. As a confirmation of this concept, the TG cases of this study with upper third involved tumor location, but tumor border of > 3 cm apart to EGJ had metastasis to each LN station similar to above-mentioned database cases (no LN metastasis in LN station #2). RFS curve also showed there was no difference of recurrence-free survival rate between PPG and other two groups. Recurrence pattern of 2 cases in PPG group showed recurrence neither in the remnant stomach nor the regional LNs demonstrates that resection margin safety of PPG is comparable to DSG and TG.

Another important part of the oncological safety considerations in the PPG group was LN station #1. Due to closeness of tumor, LN station #1 was radically resected in most cases of the PPG cohort, which is underlined by the fact that the PPG group and DSG group showed similar numbers of retrieved lymph nodes in this location and no significant differences to TG. As oncological safety was given highest priority, compromising the hepatic branch of vagus nerve was potentially expected to lead to a higher rate of delayed gastric emptying or gallstone formation [33]. The institution established measures to prevent DGE by intraoperative manual dilatation [34], that was applied in 52/145 PPG of this cohort, or early detect and efficiently treat it by radiologic balloon dilatation [35]. Interestingly, we did not find a high rate of DGE (3.4%), suggesting that preservation of the hepatic branch of vagus nerve is not essential in PPG, as this rate is even lower than the generally reported rate of 7–8% [7, 36, 37]. This hypothesis is supported by the previous studies [38, 39]. However, it has to be mentioned that our result was also influenced by the manual dilatation maneuver in 52 cases and a sufficient comparison group is lacking. Another factor to influence the rate of DGE after PPG is the antrum cuff length. It has been reported that the incidence of DGE was 35.0% (7/20) in patients with an antral cuff length of 1.5 cm and only 10.0% (1/10) in patients with an antral cuff length of 2.5 cm [40]. Nunobe et al. [41] reported an incidence of DGE of 6–8% among 90 patients after PPG in whom the antral cuff length was maintained at 3 cm. In our study, due to the high tumor location and the consecutively smallish proximal remnant stomach, the antrum cuff lengths range from at least 3 cm up to 5 cm. The length was determined by the operator, mainly influenced by distal margin of the tumor. Also due to a longer antrum cuff, tension did not appear as a problem during anastomosis.

In terms of gallbladder stone formation, we detected 3 PPG patients after a maximum of 4-year follow-up and a median follow-up of 30 months, which appears as a relatively low rate. For a conclusive statement on this, it is suggested to wait for data maturation, since the other authors found a higher gallbladder stone formation in patients with compromised hepatic branch of vagus nerve after 5 and 10 years of follow-up [39, 42]. Reconstruction of digestive tract may also contribute to higher incidence of gallstone in TG cases. Liang et al. [43] reported that reconstruction with duodenal exclusion will induce higher risk of gallstone disease, while PPG operation with gastro-gastrostomy would protect the patients from this postoperative burden.

Resection in most PPG cases in our cohort was performed laparoscopically or robotically, and showed advantages in terms of surgical outcomes compared to DSG and TG groups. The same result has also been reported in the other studies [7, 37, 44, 45]. Compared to DSG and TG cases, operative procedure is less effortful for PPG by skipping certain areas of dissection, which leads to shorter operation time and less blood loss. A lower postoperative morbidity would definitely decrease postoperative stay in hospital.

As described in the "Introduction" section, there are several advantages in functional outcome of PPG and we are waiting for the result of a prospective trial (KLASS-04) [46, 47]. In this study, PPG leads to even more advantages when being compared to TG for nutrition index and incidence of gallstone formation. Except weight loss and BMI, we choose additional serological parameters, which were more objective to evaluate the nutritional status of different gastrectomy resection types. TG cases had significantly lower values in hemoglobin, total protein, and albumin level. In fact, it was expected that nutritional and functional outcomes after PPG are better than after TG. For nutritional assessment, CT-based quantification of abdominal adipose tissue can be a useful method, which minimizes the interobserver variation and achieves reproducibility in retrospective study [48–52]. In our study, the lowest decrease rate of total abdominal fat, visceral fat, and subcutaneous fat was seen in PPG group, and it was also significantly different from that of DSG with total abdominal fat and visceral fat. This also speaks in favor of the functional or nutritional advantages of PPG operation. Furthermore, these PPG patients do not need Vitamin B12 supplementation.

As important limitation of this study, it has to be mentioned that this study is a retrospective, which cannot replace evidence from randomized-controlled trials. Especially for this very specific tumor location and operation type, prospectively standardized criteria could lead to a better comparison to other resection types. In addition, longer follow-up period would provide more information of the oncological safety of PPG in upper third involved EGC and functional long-term outcomes.

Although we are waiting for this longer follow-up period of this cohort to confirm the results, we are convinced by the benefits of PPG in patients with upper stomach EGC compared to distal gastrectomy or total gastrectomy.

Conclusions

PPG can be a good option even for upper third involving EGC in technically feasible locations. Lower postoperative morbidity, better functional outcomes, and the same oncological safety are found for PPG compared to DSG and TG.

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Compliance with ethical standards

Conflict of interest No conflict of interest exists.

Ethics statement This study was conducted in accordance with the Ethical Principles for Medical Research Involving Human Subjects, as outlined in the Declaration of Helsinki after the approval of the institutional review board of Seoul National University Hospital. Informed consent was waived by the institutional review board based on its decision that the risk of this study to the patient is minimal. The research protocol was approved by the institutional review board of Seoul National University Hospital (No. 1707-157-874).

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